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(54) **COMBINED USE OF HYALURONIC ACID AND THERAPEUTIC AGENTS TO IMPROVE THE THERAPEUTIC EFFECT**

KOMBINIERTE VERWENDUNG VON HYALURONSÄURE UND THERAPEUTISCHEN WIRKSTOFFEN ZUR VERBESSERUNG DES THERAPEUTISCHEN EFFEKTS

UTILISATION COMBINEE DE L'ACIDE HYALURONIQUE ET D'AGENTS THERAPEUTIQUES POUR AMELIORER L'EFFET THERAPEUTIQUE

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(56) References cited:
EP-A- 0 138 572
EP-A- 0 197 718
EP-A- 0 216 453
EP-A- 0 224 987
EP-A- 0 265 116
US-A- 4 711 780

- **CHEMICAL ABSTRACTS, vol. 76, no. 10, 6 March 1972, Columbus, Ohio, US; abstract no. 49897f, SNEADER ET AL 'POSSIBLE MECHANISM FOR THE ACTION OF DIMETHYL SULFOXIDE ON PERCUTANEOUS ABSORPTION' page 273 ;column 2 ; & J.PHARM.PHARMACOL., vol.23(S), 1971 page 252S**

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Description

FIELD OF INVENTION

[0001] The invention relates to the use of certain medicinal and/or therapeutic agents and hyaluronic acid and/or sodium hyaluronate in the manufacture of a pharmaceutical composition for treating certain diseases or conditions in a therapy.

BACKGROUND OF THE INVENTION

[0002] In an article entitled "Solid cores of tumors keeping out best drugs" by Sandra Blakeslee published in the July 8, 1989 edition of the Globe and Mail, Toronto, Ontario, Ms. Blakeslee submitted that a growing number of researchers believe that a basic misunderstanding of the structure of solid tumors has led researchers into designing cancer drugs that are doomed to fail in many patients.

[0003] She relates that, Dr. Herberman, Director of the Pittsburgh Cancer Center, said that for decades, cancer researchers have simply developed drugs, put them in the bloodstream and assumed they would be carried to the tumor giving almost no consideration to how uniformly the drug is distributed once it reaches the tumor.

[0004] Her article also provided that according to Dr. Judah Folkman, a leading researcher on blood growth factors at the Harvard Medical School, for a long time, physicians have been taught that tumors outgrow their blood supply. According to the article that statement is not true. Tumors compress their blood supply. This compression makes it harder to administer drugs.

[0005] The article provides further that most people think a tumor is nothing but a collection of cancer cells. According to Dr. Jain, another researcher, in reality the tumor is only 50 per cent cells. The other half is blood vessels and interstitial space. Interstitial space in a tumor, he said, can be likened to the space between marbles packed in a box.

[0006] The article further provides that no matter how biological agents are mixed and administered, they must cross a blood-vessel wall and then cross the interstitium to reach their targets, cancer cells. The article continues that every tumor is different and there are different regions within each. Moreover, tumors change daily as they grow and rearrange parts. Most blood vessels inside tumors are highly disorganized as they take tortuous turns and grow peculiar attachments to nearby vessels.

[0007] In general, Dr. Jain said, as a tumor grows, its outer region recruits new blood vessels from surrounding normal tissue. It also forms several abnormal blood vessels of its own. As the tumor grows in a confined space, many of the twisted blood vessels near its center are crushed. In turn, the tumor cells near them appear to die, although they grow into active cancer if transplanted in other animals. High pressures build up in these necrotic regions. Both blood vessels and liquid plasma in the interstitial spaces are squeezed. The pressure, therefore, prevents blood-borne molecules, including oxygen, from entering the central tumor areas.

[0008] Pressure is not uniform in normal tissue, Dr. Jain said, so a large molecule such as an antibody would reach its target through convection induced by pressure differences. But in the center of a tumor, pressure is uniformly high, blocking convection.

[0009] Molecules also migrate by diffusion Dr. Jain said, which is similar to the way a drop of ink spreads in water.

[0010] But he indicated that he measured antibody diffusion in tumors and found that it can take days, weeks or months for such large molecules to reach uniform concentration by diffusion in tumors. By then, it may be too late for treatments to do any good.

[0011] Finally, the fluid that builds up in the interstitium slowly leaks out of the tumor, he said, washing away molecules trying to reach its center.

[0012] In our Canadian Patent Number 1,319,107 we disclose a new formulation suitable for use for treating cancer (for use in conjunction with at least thermotherapy (hyperthermia) and if desired, other modalities (such as chemotherapy or radiation)), the formulation comprising (for example in a pharmaceutically acceptable carrier):

(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and
(b) an effective (non-toxic) amount of an agent which (i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and (ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

[0013] We also disclosed a combination and formulation suitable for use for treating cancer, the combination comprising:

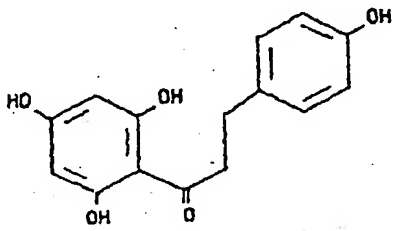
(a) a glucose inhibiting (non-toxic) amount to an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and
(b) an effective (non-toxic) amount of an agent which (i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and (ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

[0014] After the introduction of the formulation or combination comprising agents (a) and (b) to the patient which have the effect of metabolically compromising the cancer cells of the tumor, the tumor and the cancer cells making up the tumor are stressed by at least thermotherapy (hyperthermia). In this regard, when agent (a) is transported into the tumor cells and the tumor cells are stressed, there is an inadequate amount of glucose available to the tumor cells for them to continue to function metabolically. Thus the tumor cell is impaired in its energy supply and dies. We also disclosed in the application a method for the treatment of cancer which method comprises administering (for example in a pharmaceutically acceptable carrier):

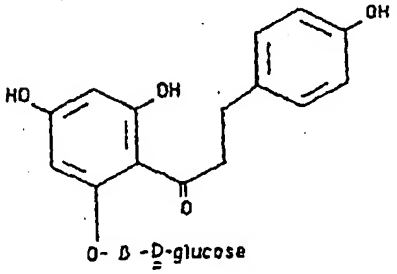
(a) a glucose inhibiting (non-toxic) amount of an agent that blocks the glucose transport protein (active transport molecule in the membrane) of a cell from transporting glucose into the cell, and
(b) an effective (non-toxic) amount of an agent which (i) enhances penetration and transporting of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and (ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor, and subjecting the cancer cells to hyperthermia (thermotherapy) therapy. In some instances other modalities (for example chemotherapy and/or radiation therapy) may also be employed.

[0015] The glucose inhibiting (non-toxic) amount of the agent that blocks the glucose transport protein of a cell from transporting glucose into the cell (in cancer cells there appear to be more than in normal cells) may comprise:

Phloretin



Phloridzin



or their analogues including phlorizin glucuronide; 4-deoxy-phloretin-2-D-glucoside and the like.

[0016] The effective (non-toxic) amount of the agent which

(i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements generally known as scar tissue or fibrous reaction around the cancerous tumor, and
(ii) alters the penetration characteristics of the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor may comprise dimethyl sulfoxide (DMSO), methylsulfonylmethane (MSM) (also called methylsulfone methane) or other carrier transport-type molecules having the characteristics which

(i) enhances penetration and transport of agent (a) through the tissue surrounding the various cellular elements, generally known as scar tissue or fibrous reaction around the cancerous tumor, and
(ii) alters the penetration characteristics of-the tissue surrounding the tumor to permit agent (a) to be transported to the center of the tumor.

[0017] In the publication Ontario Medicine, Volume 8, No. 16 dated August 21, 1989 the article "Toxic drug tamed but still potent" describes how an experimental liposomal drug delivery system, is used to encapsulate a highly toxic but highly effective anti-fungal agent, demonstrating that noxious drugs can be transformed into non-toxic agents without compromising clinical efficacy.

[0018] The article concluded as follows:

[0019] "It was initially hoped that liposomes would offer considerable potential as a drug delivery system for almost all pharmaceutical agents. However, research into the drug delivery system over the past two decades has shown that the artificial, cell-sized spheres form spontaneously with only a small subset of drugs available today thus limiting their use."

[0020] Hoffer in a study explored the effects of ascorbic acid (Vitamin C) in respect of the health of patients. In the article he discussed the effects of Vitamin C with respect to cancer treatment. He also discussed the findings of Cameron and Pauling of the use of ascorbic acid in 10 gram doses to treat cancer patients and which administration of the ascorbic acid increased the survival of terminally ill cancer patients. Be also discussed the safety of the use of ascorbic acid and the saftey in very high doses. He stated at page 11 of his study that the ascorbic acid was water soluble, was bulky but had no LD-50. Hoffer states that

" When the vitamin cannot be absorbed completely from the gastrointestinal system, it will remain water in the bowel leading to diarrhea, which is watery but not dangerous unless it causes dehydration; it quicky forces patients to decrease the doses. It has and is being used by millions of people in these doses. Patients I have known have taken 30 grams per day for 30 years. It is safer than common table salt, gram for gram. It does not cause kidney stones, does not cause pernicious anemia, does not make women infertile, does not cause cancer."

[0021] It is therefore an object of this invention to provide means suitable for the treatment of certain diseases and conditions, and the delivery of certain medicinal and therapeutic agents for the treatment of said diseases and conditions.

[0022] Further and other objects of the invention will be realized by those skilled in the art from the following disclosure.

[0023] Hyaluronic acid is a naturally occurring glycosaminoglucan. Its molecular weight may vary from 50,000 dalton upwards, and it forms highly viscous solutions. As regards the actual molecular weight of hyaluronic acid in natural biological contexts, this is still a matter of much uncertainty: When the molecular weight of hyaluronic acid is to be determined, different values are obtained depending on the assay method employed, and on the source, the isolation method etc. The acid occurs in animal tissue, e.g. spinal fluid, ocular fluid, synovial fluid, cockscombs, skin, and also in some streptococci. Various grades of hyaluronic acid have been obtained. A preparation with an allegedly high degree of purity and alleged to be entirely free from side effects, is a non-inflammatory form described in U.S. Patent No.4,141,973; this preparation is said to have a molecular weight exceeding 750,000 dalton, preferably exceeding 1,200,000 dalton and is suggested for therapeutic use in various articular conditions.

[0024] United States Patent 4,801,619 relates to hyaluronic acid administered intra-articularly having a molecular weight of about 3×10^6 dalton or more, which is prone to decrease the proteoglycan content of synovial fluid to almost normal levels. According to this patent, this indicates a positive effect on the proteoglycan metabolism of a joint. According to the Patent this is applicable both to inflammatory conditions and to degeneration caused by treatment with symptomatics, such as corticosteroid preparations. It is thus clear that a sufficiently high molecular weight of the hyaluronic acid is alleged to counteract side effects that might be caused by corticosteroids or other symptomatics producing similar effects. When corticosteroids are applied, the amount of hyaluronic acid in the synovial cavity will according to the Patent increase substantially and according to the inventors their hyaluronic acid preparations have a very positive effect on such clinical symptoms as pain, swelling and lameness.

[0025] The patent states that the objectives of the invention are attained by intra-articular administration of an effective amount of hyaluronic acid with a mean molecular weight exceeding 3×10^6 dalton, preferably exceeding 4×10^6 dalton; usually the molecular weight will not exceed 7×10^6 dalton. The dosage of hyaluronic acid administered is stated to be preferably within the range of 5mg-80mg. The amount of solution given at each administration is generally less than 60 ml, e.g. less that 20 ml, of an aqueous solution of the acid or its salt. It is convenient to administer the acid dissolved in water (<2% w/w, buffered to physiological pH), for instance in the form of a water-soluble sodium salt. The exact amount will depend on the particular joint to be treated.

[0026] The Merck Index Specifies that Hyaluronic Acid has a Molecular Weight within the range pf 50,000 to 8×10^6 depending on source, methods of preparation and methods of determination. The Merck Publication teaches hyaluronic acid as a surgical aid (ophthalmological).

[0027] United States Patent 4,808,576 purports to teach that hyaluronic acid, an agent well known to reduce the sequelae of trauma in mammalian joint tissue when applied directly to the traumatized tissue, will be carried to such traumatized tissue by the mammal's natural processes if applied at a site remote from the traumatized tissue. Thus hyaluronic acid in any therapeutically acceptable form can, according to the Patent, be administered by the typical remote routes including intravenous, intramuscular, subcutaneous and topical.

[0028] This, the patent alleges, makes the utilization of hyaluronic acid much more convenient and attractive. For instance the treatment of arthritis in horse or human joints with hyaluronic acid according to the patent no longer requires more difficult intra articular injections.

[0029] United States Patent 4,725,585 relates to a method of enhancing or regulating the host defence of a mammal, said method comprising administering to a mammal a therapeutically effective amount of hyaluronic acid.

[0030] At column 1 lines 43 - 46, the patent provides that the invention was based on the unexpected discovery that administration of hyaluronic acid to mammals results in a considerable increase in the defence.

[0031] The hyaluronic acid employed in the Patent was Healon (T.M.) provided by Pharmacia AB, Uppsala, Sweden (Pharmacia AB is also entitled to the benefit of United States Patent 4,141,973). The patent provides at column 4, line 19 that because a patient's infections had been hard to treat, instead of just hyaluronic acid being administered to the patient to increase the patient's defence, the patient was given hyaluronic acid and an antibiotic. While the patent states that the antibiotic was given in combination with hyaluronic acid, in fact because the hyaluronic acid was administered subcutaneously and because the patient was a heart patient, one skilled in the art would understand that any antibiotic administered, while possibly administered simultaneously was definitely administered separately intravenously (probably) or intramuscularly (less probably). Thus, (most probably) the hyaluronic acid administered according to the teachings of this patent was administered in order to prevent possible development of infections (increase the host's defence) and not for any other reason.

[0032] United States Patent 4,636,524 discloses cross-linked gels of hyaluronic acid, alone and mixed with other hydrophilic polymers and containing various substances or covalently bonded low molecular weight substances and processes for preparing them. These products are alleged to be useful in numerous applications including cosmetic formulations and as drug delivery systems.

[0033] The patent further states that as hyaluronic acid is known to be a biologically tolerable polymer in the sense that it does not cause any immune or other kind of response when introduced into a human body, the cross-linked hyaluronic acid gels can be used for various medical applications. The cross-linked gels modified with other polymers or low molecular weight substances it is alleged can be used as drug delivery devices. For example, the inventors are alleged to have found that heparin introduced in a cross-linked hyaluronic acid gel retained its antithrombogenic activity.

[0034] The inventors also allege that they have also found that cross-linked gels of hyaluronic acid can slow down the release of a low molecular weight substance dispersed therein but not covalently attached to the gel macromolecular matrix.

[0035] Unites States Patent 4,736,024 purports to teach new medicaments for topical use containing:

(i) an active pharmacological substance or a mixture of pharmacological substances, either active or suitable for topical administration and

(ii) a topical vehicle which comprises hyaluronic acid or a molecular fraction of hyaluronic acid or a salt of the same with an alkaline metal, an alkaline earth metal, magnesium, aluminium, ammonium or a pharmacological substance, optionally together with additional conventional excipients for pharmaceutical preparations for topical use.

[0036] Applicants are also aware of recently published Japanese Patent Document 61000017 dated 86/01/06 whose English abstract of disclosure states that the Japanese Patent Document relates to the use of hyaluronic acid or cross-linked hyaluronic acid or their salts as the active ingredient for inhibiting carcinoma metastasis.

[0037] According to the purported abstract of the Patent more that 1.0% of hyaluronic acid is dissolved in alkaline aq. soln. and pref. more than 50% of H_2O sol. org. solvent. eq. alcohol, acetone, dioxane, against total soln. is added. Preferably the pH is 12-14. Then multifunctional epoxy cpd. is added and reacted at 10-60 deg. C, pref. at 20-40- deg. C for 24 hrs. Cross-linking ratio of crosslinked hyaluronic acid or its salt is regulated by changing mol ratio of hyaluronic acid or its salt and multifunctional epoxy cpd.. Pref. hyaluronic acid used has intrinsic viscosity 0.2-30,m.w. 4000-2000000. The hyaluronic acid is allegedly used in several dosage forms. Clinical dose for adult is alleged to be normally, as hyaluronic acid or cross-linked hyaluronic acid, 25mg-5 g/day (p.o.) and 10 mg-2.5 g/l dose (inj). The abstract alleges that the advantage is that the hyaluronic acid has no side effects as other anticancer drugs and has an analgesic and a tissue restoration effect.

[0038] European Patent Application 0295092 purports to teach a vehicle together with fragments of hyaluronic acid for delivering of the fragments of hyaluronic acid into the skin to reach the dermal layer of the skin to increase the development of blood vessels for stimulating hair growth or regrowth. The preferred fragments of hyaluronic acid are polysaccharides containing from 7 to 25 monosaccharide units. The patent provides it is apparent that the larger the

fragments of hyaluronic acid, the greater the difficulty there is in delivering the fragments to the dermal layer of the skin, unless there is also present in the composition a means for enhancing the activity of said fragments.

[0039] The combination may thus include a means for enhancing the activity of the fragments of hyaluronic acid especially to improve their penetration through the skin following topical application. Some activity enhancers, it is alleged, also function as vehicles for the fragments of the hyaluronic acid.

[0040] Some activity enhancers are also alleged to possess the ability to stimulate or increase hair growth. Minoxidil is asserted among others to be such an activity enhancer. Thus both the fragments of hyaluronic acid and minoxidil are alleged to stimulate hair growth both delivered by a vehicle.

[0041] European Patent Application 0179442 asserts that where free radicals are formed in considerable quantities, hyaluronic acid is broken down or degraded before the hyaluronic acid has given the desired effect.

[0042] Canadian Letters Patent 1,240,929 teaches the combination of chondroitin sulfate compound and a hyaluronate to protect both human and animal cell layers and tissue subject to exposure to trauma.

[0043] European Patent Application 0208623 purports to teach hyaluronic acid as une augmentation de l'activite de certaines proteases. It also purports to teach the use of hyaluronic acid for treating connective tissue diseases including malignant tumors and cardiovascular disorders.

[0044] European Patent Application 270317 purports to teach the combination of an antiviral agent lacking inhibitory action and a compound [for example, hyaluronic acid] possessing cell fusion inhibitory activity and/or virus-adsorption inhibitory activity for treating disease carried by a virus.

[0045] United States Patent 4,840,941 purports to teach the use of an effective amount of hyaluronic acid as the active agent for the treatment of retroviruses in association with a pharmaceutically acceptable carrier, diluent or excipient.

[0046] United States Patent 4,851,521 and European Patent Application 0265116 both describe hyaluronic acid fractions, the making thereof and cross-linked esters of hyaluronic. United States Patent 4,851,521 describes esters of hyaluronic acid incorporated into pharmaceutical preparations as the active ingredient and as vehicles for ophthamological medicines for topical use (See column 11, lines 35 to 42; and column 12, lines 62 to column 13, line 3) and in suppositories for a systemic effect due to the effect of transcutaneous absorption, such as in suppositories.

[0047] The patent provides at column 13, lines 5 to 31:

> "The vehicling action of the hyaluronic esters also applies to associated medicaments of the type mentioned above in which the active substance acts not only topically or by nasal or rectal absorption, for example by nasal sprays or preparations for inhalation for the oral cavity or the pharynx, but also by oral or parenteral route, for example by intramuscular, subcutaneaous or intravenous route, as it favors absorption of the drug into the application site. The new medicaments can therefore be applied, apart from in the fields already mentioned, in practically all sectors of medicine, such as internal medicine, for example in pathologies of the cardiovascular system, in infections of the respiratory system, the digestive system, the renal system, in diseases of an endocrinological nature, in oncology, in psychiatry etc., and may also be classified therefore from the point of view of their specific action, being perhaps anesthetics, analgesics, anti inflammatories, wound healers, antimicrobics, adrenergic agonsits and antagonists, cytostatics, antirheumatics, antihypertensives, diuretics, sexual hormones, immunostimulants and immunosuppressants, for example, one of the drugs having the activity already described for the therapeutically active alcohols to be used as esterifying component according to the present invention, or for the therapeutically active bases used for the salification of the free carboxylic groups."

[0048] Furosemide inhibits sodium reabsorption in the ascending limb of Henle's Loop and in both proximal and distal tubules. The action of the drug is independent of any inhibitory affect on carbonic anhydrase or aldosterone. Furosemide is known to promote diuresis in cases which have previously proved resistant to other diuretics. It has no significant pharmalogical effects other than on renal function. In the human it is absorbed from the gastrointestinal tract. Following intravenous administration a diuresis generally occurs within 30 minutes and the duration of action is about 2 hours.

[0049] Under a variety of circumstances, the patient can become relatively resistant to the effects of Lasix. This can be so for a variety of reasons but is certainly seen in those situations where there is a major amount of peripheral edema or "third spacing" of fluid which may be true in malnutrition and/or advanced carcinomas. In the latter instances, there is a markedly decreased level of albumin and in all probability, increased permeability and transudation of fluid out of the vascular system. Hence, these patients can become relatively resistant to any of the diuretics including high doses of Lasix administered intravenously.

[0050] There have been extensive studies to determine the defect in immune function that allows a tumor cell to develop. It was postulated initially by Jerne, and subsequently by Burnett that the immune system's major role was that of immunological surveillance to destroy abnormal cells. The concept of surveillance, while somewhat simplistic, remains an accepted concept for the elaborate mechanism of immune recognition and function that is present in the

higher species - mammals.

[0051] It has then been postulated that tumors develop because of local or generalized immune suppression. However, as pointed out by Moller, if general immune suppression occurs, it is only certain types of neoplastic disorders that develop, mainly those of the lympho-reticular system. This observation is correct and represents a major challenge to the immune surveillance theory unless a specific reason can be shown as to why the individual cancer cell can develop plus individually evade the immune system.

[0052] It was demonstrated experimentally in 1974 that defects of macrophage function may exist in neoplastic disease.

[0053] The initial experiments found suppressor cells to be part of the immune system; these were either of the T-cell type of the macrophage cell system. There was presence demonstrated in neoplasia, chronic bacterial infection, recovery from massive injury and chronic fungal infection.

[0054] There has been repeated demonstration in experimental animals, that the macrophage cell function is altered in neoplastic disease. The macrophages in the animal's systems appeared "blocked" in their function. Generally when removed from the in vivo situation, washed in saline and cultured, they could perform normally. This block has been shown to be related to the excessive production of prostaglandin by neoplastic tissue or by the macrophage itself.

[0055] In the basic research efforts in the latter '70s and the early 80's, there existed considerable confusion as to what role immunotherapy should take in cancer. Activation or "hyping" of macrophages was thought to be important. However, in an examination by Romans and Falk of peritoneal macrophages obtained from patients with neoplastic disease, there was definite evidence that these macrophages were already activated yet were co-existing with cancer cells and not causing their destruction.

[0056] In the early part of this year it has been shown by several independent investigators that the malfunction of macrophages or the putitive block is due to excessive prostaglandin and that this can be altered in tissue culture by corticosteroids, ASA, and the non-steroidal anti-inflammatory drugs, i.e. indomethacin, and naproxen (Naprosyn™). Again, in animal tumors it was repeatedly demonstrated that these substances could alter the response to neoplastic cells and that various combinations of these substances employed with immune enhancing agents could produce very credible success in eliminating experimental tumors. Lala and co-workers combined Indomethacin therapy with Interleukin 2 and showed that this could effect a cure with experiment neoplasm.

[0057] There were continued problems with the use of any of these agents in the actual human in vivo experience. All of the non-steroidal anti-inflammatory agents (NSAID) produced major toxicity in terms of gastro-intestinal, neurological, and other areas. Thus, the basis of the present approach is that under general circumstances the use of these agents in human disease, in sufficient amounts, the drug will penetrate to any pathological tissue to alter therapeutically local prostaglandin production. While intravenous preparations exist of Indomethacin and now of other agents, the data is overwhelming, as is our own experience, that using these drugs alone produces prohibitive side effects in human subjects. Therefore only insufficient amounts can be brought into the body to effect more than occasional responses in neoplasm.

[0058] However the majority of the evidence is present to indicate and therefore it can be postulated that the basis for neoplastic development and how the initial cell "sneaks by" the immune surveillance mechanism relates to its production of prostaglandin. One need postulate only one mutation to alter the amount of prostaglandin synthesis produced by cells when they become "malignant" to establish a mechanism of blocking out the initial cell in any immune reaction, i.e. the macrophage. It therefore became essential to develop a combination of NSAIDS for clinical use to produce a major improvement in response in neoplastic disease and other conditions where excessive prostaglandin synthesis represents the basis of the pathogenesis of this disease state, i.e. arthritis, and various others of the so-called connective tissue inflammatory disorders and/or auto-aggressive diseases.

[0059] See also:

1. Modulation of Immunity in Cancer Patients by Prostaglandin Antagonists, Immunity to Cancer II, Alan R. Liss, Inc.; and
2. Goodwin, J.S. (1981) Prostaglandin E and Cancer Growth Potential- for Immunotherapy with Prostaglandin Synthesis Inhibitors, Augmentive Agents in Cancer Therapy, Raven Press, New York.

[0060] United States Patent 4,711,780 teaches a pharmaceutical composition comprising Vitamin C, a zinc salt, a sulfur amino acid for treating surface epithelium for epithelium regeneration. Hyaluronic acid may be added for applications in the reproductive tract.

[0061] Japanese Patent Publication 63/045223 relates to the treatment of disease caused by retroviruses. Hyaluronic acid is taught for prevention or therapy of leukemia or AIDS by suppressing replication of the virus.

[0062] An article entitled "Inactivation of Herpes Simplex Viruses by Nonionic Surfactants" by one of the inventors herein (Dr. Samuel Asculai) among others [published in Antimicrobial Agents and Chemotherapy, April 1978, pp. 686-690] disclosed nonionic surface-active agents, for example nonoxynol-9 found in Delfen™, "possessing ether or

amide linkages between the hydrophilic and hydrophobic portions of the molecule rapidly inactivated the infectivity of herpes simplex viruses. The activity stemmed from the ability of nonionic surfactants to dissolve lipid-containing membranes. This was confirmed by observing surfactant destruction of mammalian cell plasma membranes and herpes simplex virus envelopes. Proprietary vaginal contraceptive formulations containing nonionic surfactants also inactivated herpes simplex virus infectivity. This observation suggests that nonionic surfactants in appropriate formulation could effectively prevent herpes simplex virus transmission."

SUMMARY OF THE INVENTION

[0063] Applicants have now discovered uses in accordance with the invention which are specified in claim 1. Said uses employ as the case may be a therapeutically effective non-toxic amount of a medicinal and/or therapeutic agent suitable to treat the disease or condition for example ascorbic acid (Vitamin C) (for the treatment of mononucleosis), a nonionic surfactant, e.g. nonoxynol-9 [nonylphenoxy polyethoxy ethanol] found in Delfen™ contraceptive cream, non-steroidal anti-inflammatory drugs (NSAID) for example indomethacin, naproxen and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) detoxifying agents (for example for administration rectally in an enema), bronchodilator, anti-bacterial agent, antibiotics, drugs for the treatment of vascular ischemia (for example diabetes and Berger's disease), minoxidil for topical application for hair growth, diuretics (for example furosemide (sold under the trademark Lasix™)), cyclosporins, in combination with an amount of hyaluronic acid and/or sodium hyaluronate sufficient to provide a dosage greater than 10mg/70 kg person and to facilitate the agent's penetration through the tissue (including scar tissue), at the site to be treated through the cell membranes into the individual cells to be treated. When such combinations are administered to patients suffering from the disease or condition, the disease or condition is unexpectedly improved.

[0064] The combination can be administered among other methods, intravenously, intra arterially, intraperitoneally, intrapleurally, transdermally, on the skin (topically), rectally, orally or by direct injection (for example into an abscess or similar disease focus) or put on a patch to be secured to the skin of the patient. The hyaluronic acid and/or sodium hyaluronate and the agent can be administered separately but are administered in sufficient amounts and in an immediate time sequence or interval (preferably concurrently and more preferably simultaneously), preferably at the identical site (e.g. one given intravenously and the other "piggy backed"), to treat the disease or condition.

[0065] According to the invention there is provided the use of:

(1) a medicinal and/or therapeutic agent and
(2) hyaluronic acid and/or sodium hyaluronate in the manufacture of a pharmaceutical composition for treating a disease or condition in a therapy wherein a therapeutically effective amount of said medicinal and/or therapeutic agent (component (1)) is administered to a human, together with the hyaluronic acid and/or sodium hyaluronate in an amount sufficient to provide a dosage greater than 10mg/70kg person characterised in that the amount of component (2) is immediately available to transport component (1) at the site to be treated, and, is an effective non-toxic amount to facilitate the transport of component (1) through the tissue (including scar tissue) at the site to be treated and through the cell membranes at the individual cells to be treated, and in membranes at the individual cells to be treated, and in that:

(i) when the disease or condition is herpes canker sores or shingles, component (1) is a non-ionic surfactant;
(ii) when the disease or condition is renal failure, cardiac insufficiency, hypertension and edema, component (1) is a diuretic;
(iii) when the disease or condition is infection or acne, component (1) is an agent selected from antibiotics, antibacterials and antimicrobials;
(iv) when the disease or condition is mononucleosis, component (1) is ascorbic acid;
(v) when the disease or condition relates to the transplantation of an organ, component (1) is a cyclosporin;
(vi) when the disease or condition is inflammation or pain, or arises from toxins and debris resulting from tumour breakdown or requires the decrease of side effects of giving an NSAID, component (1) is an NSAID;
(vii) when the disease or condition is the toxification of the body, component (1) is a detoxifying agent;
(viii) when the disease or condition requires bronchodilation, component (1) is a bronchodilator;
(ix) when the disease or condition is vascular ischemia, component (1) is trental;
(x) when the disease or condition is HIV or AIDS, component (1) is selected from the agents consisting of Ascorbic Acid, NSAID, doxocycline, tetracycline and combinations
(xi) when the disease or condition is diabetes, component (1) is insulin;
(xii) when the disease or condition is topical infection or the prevention thereof, component (1) is an antimetabolite;
(xiii) when the disease or condition is post-menopause, component (1) is an estrogen replacement;

(xiv) when the disease or condition is hypertension or cardiac insufficiency, component (1) is a calcium channel blocker;
(xv) when the disease or condition requires prostaglandin synthesis inhibition, component (1) is an NSAID;
(xvi) when the disease or condition requires enhanced oxygenation of tissue by perfusion fluid, component (1) is perfusate; and
(xvii) when the disease or condition is psoriasis, component (1) is methotrexate.
(xviii) when the disease or condition is hair loss, component (1) is minoxidil.

[0066] Preferred embodiments of the invention are as set out in the appended claims. In these embodiments, the NSAID may be diclofenac, indomethacin, piroxicam, ibuprofen, tromethamine salt of ketorolac or naproxen and the bronchodilator may be beclomethasone diproprionate, theophylline or sodium cromoglycate.

[0067] The medicinal and/or therapeutic agent may be for example ascorbic acid (Vitamin C) (for the treatment of mononucleosis), a nonionic surfactant, e.g. nonoxynol-9 [nonylphenoxy polyethoxy ethanol] found in Delfen™ contraceptive cream, non-steroidal anti-inflammatory drugs (NSAID) for example, indomethacin, naproxen and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) detoxifying agents (for example for administration rectally in an enema), bronchodilator, anti-bacterial agent, antibiotics, drugs for the treatment of vascular ischemia (for example diabetes and Berger's disease), minoxidil for topical application for hair growth, diuretics (for example furosemide (sold under the trademark Lasix™)), and cyclosporins.

[0068] Applicants postulate that the hyaluronic acid and/or sodium hyaluronate facilitate the transport of the agent to the site to be treated and to penetrate the tissue (including scar tissue) through all membranes in the individual cells to be treated.

[0069] By way of example and to illustrate the facilitation of the delivery or transport of a chemical to a site in a mammal, when ethyl alcohol is injected directly into a tumor, and sonographic (ultrasound) assessment is made, it is not dispersed throughout the tumor. When the ethyl alcohol to be administered into a tumor is carried by hyaluronic acid and/or sodium hyaluronate, sonographic assessment of the tumor demonstrates the dispersion of the ethyl alcohol throughout the tumor.

[0070] While Applicants postulate that the hyaluronic acid facilitates the transport and delivery, Applicants' invention may be used as described irrespective of the actual method of operation of the hyaluronic acid and/or sodium hyaluronate The combination of hyaluronic acid and sodium hyaluronate with different chemicals and drugs (Vitamin C, etc) alters their distribution and performance in the human body and produces an unusual targeting for underperfused tissue and/or pathological tissue. In this regard the use of ascorbic acid (Vitamin C) as a free radical scavenger (50 gm daily - 1000 times the daily dose in therapeutic purposes as a vitamin) administered intravenously with 300 - 500mg of hyaluronic acid (sodium hyaluronate) immediately relieves bone pain and muscle pain and reduces inflammation in cancer patients. The hyaluronic acid enhances the anti-neoplastic activity and effect of the ascorbic acid. It is thought that this enhanced activity eliminates the free radicals by acting as a free radical scavenger. In any event the patients feel better. This is also demonstrated with furosemide and hyaluronic acid where the activity of furosemide is enhanced only minimally when administered with hyaluronic acid to a "normal" subject but the activity is enhanced significantly when administered to a patient whose kidney is underperfused or malfunctioning due to insufficient intra-vascular volume.

[0071] A similar situation occurs with the NSAIDS. As a major amount of soluble indomethacin is required, the chemical product was solubilized using n-methyl glucamine at a dilution of 5mg/ml of n-methyl glucamine (NMG). This substance is then passed through a 22 micron Milipore filter to produce sterility. This material is non-toxic at 16 fold the therapeutic dose in animals and for this reason was considered appropriate to be used in human conditions. Thus, Indocid™ solubilized in NMG is administered to human patients either into the tumor intraperitoneally, intrapleurally, or intravascularly at a varying dose up to 10 mg/kg where each dose of indomethacin is combined with 200 - 1000mg of hyaluronic acid (for example "LifeCore™" hyaluronic acid [sodium hyaluronate]) diluted in the original solution of indomethacin and NMG with for example the "LifeCore™" hyaluronic acid. This produces an appropriate mixture and can be administered safely by any of the routes. [Similar clinical studies have been done with hyaluronic acid prepared by other methods, i.e. extraction. The extracted material is satisfactory to use for intratumor, intraperitoneal or intrapleural use with this substance.]

[0072] Thus and according to another aspect of the invention when an NSAID for example indomethacin (dissolved in n-methyl glucamine) or other NSAID is administered with greater than 200mg hyaluronic acid for 1 - 2 mg/kg body weight of the NSAID (in one instance indomethacin and NMG), no major toxic side effects occur such as gastro-intestinal distress, neurological abnormalities, depression, etc., even at elevated amounts of indomethacin (if necessary). If the amount of hyaluronic acid is decreased below that amount, the usual side effects may begin to reoccur. In addition, the responses that have been observed are superior when the NSAID (for example Indocid™) is combined with hyaluronic acid demonstrating clearly that the combination is now "targeting" to the pathological tissue even when administered by the systemic intravenous route. Thus, it has been observed that patients with neoplastic diseases when

receiving in addition to other chemicals (for example ascorbic acid [Vitamin C], phloretin and anti-cancer drugs), 50 - 200 mg NSAID - hyaluronic acid (sodium hyaluronate) (for example indomethacin and hyaluronic acid) experience dramatic relief of pain immediately. This is followed within a short period of time by a resolution and resorbtion of neoplastic lesions with an improvement of pulmonary, and liver function if there is tumor present in these organs. Thus the dead tumor material and the debris and tumor toxins appear to be better eliminated by the body through the action of the macrophages whose activity is enhanced by the addition of the NSAID (or a steroidal anti-inflammatory drug) administered with hyaluronic acid (or salt or other form thereof). Thus Applicants believe that the addition of the NSAID for example with hyaluronic acid (sodium hyaluronate) deblocks the macrophages by preventing enzymatic production of prostaglandin synthetase which blocks macrophage functioning. Thus the hyaluronic acid (and sodium hyaluronate) not only enhance the activity of the NSAID but also reduce any side effects and toxicity that is associated with the use of the prostaglandin synthesis inhibitors.

[0073] In one instance, as illustrative example not falling within the scope of the claims, methotrexate has been administered with hyaluronic acid over an area of tumor tissue, (e.g. the chest wall) for a period of 5-7 consecutive days. The patient's hemotological indices were lowered at least comparable to methotrexate being given at the same doses either intravenously or orally.

[0074] Further when the cancerous tumor breaks up (after treatment as previously described) in many instances the liver cannot cope with the tumor toxins and debris and residue, killing the patient. Not only is the use of hyaluronic acid with an NSAID appropriate, so is the use of enemas employing hyaluronic acid (sodium hyaluronate) and a detoxifying agent administered into the large bowel.

[0075] The hyaluronic acid and sodium hyaluronate may be utilized at varying doses - 10 to 1000 mg/70 kg person with the optimal doses tending to range between 50 and 350 mg/70 kg individual. As there is no toxicity, the hyaluronic acid can obviously be administered in a dose excess (for example 3000 mg/70 kg individual) without any adverse effects.

[0076] Intradermal delivery of other drugs may also be accomplished with hyaluronic acid and/or sodium hyaluronate: for example insulin in diabetes, estrogen in post - menopausal women, progestegens in control of fertility and anti-metabolites for the prevention of topical infection such as those caused by coryne bacterium acnes. They may also be applied using hyaluronic acid.

[0077] Intravenous administration of bronchodilators may also (for example aminophylline and theophylline) may also be accomplished with hyaluronic acid and/or sodium hyaluronate.

[0078] Enhancement of the effect of the bronchodilators by administration with hyaluronic acid has been the result. Oral administration with hyaluronic acid and/or sodium hyaluronate may also be suitable.

[0079] According to the invention, the combination of a non-ionic surfactant for example nonoxynol-9 [nonylphenoxy polyethoxy ethanol] [found in Delfen (t.m.) contraceptive cream] and hyaluronic acid and/or sodium hyaluronate is provided for treating:

(a) herpes simplex type I and type II
(b) herpes zoster (shingles)

and unexpectedly provide immediate relief of symptoms and subsequent disappearance of lesions.

[0080] The non-ionic surfactant preferably comprises an ether or an amide linkage between the hydrophilic and hydrophobic portions of the molecule, being more active than the surfactants having an ester - or an ether- ester linkage.

[0081] The following nonionic surfactants and identified linkages are offered for consideration.

Surfactant	Linkage
None (control virus)	
5% Nonoxynol-9 (nonylphenoxy-polyethoxy ethanol)	Ether
1% Triton X-100 (p-diisobutylphenoxy-polyethoxy -ethanol)	Ether
1% Brij-97 (polyoxyethylene (10) oleyl ether)	Ether
1% Span-20 (sorbitran monclamate)	Ester
1% Span-80 (sorbitan moncoleate)	Ester
1% Tween-20 (polysorbate 20)	Ether-ester
1% Tween-80 (polysorbate 80)	Ether-ester
1% Onyxol 345	Amide

[0082] Where foreign objects (for example drainage tubes) must be implanted into a human body and be left for use, it is imperative that the tissue surrounding the implant not become infected because once the tissue becomes infected,

usually no matter how much antibiotic is administered the infection does not clear and the implant must be removed. Applicants have found however that where the infected tissue surrounding the implant is treated with the antibiotic carried in hyaluronic acid (sodium hyaluronate), the infection rapidly clears and the implant need not be removed.

[0083] Applicants have also found that in respect of treating vascular ischemia (for example in cancer patients where the tumor tissue is under perfused, in patients suffering from diabetes and Berger's disease), the administration of the medicines in hyaluronic acid (sodium hyaluronate) enhances the patient's response to the drug.

[0084] In patients suffering from brain tumors, the swelling must be reduced. Administration of dimethyl sulfoxide (DMSO) in amounts of less than 100 gm daily in a 10% solution in hyaluronic acid (sodium hyaluronate) -300 - 500 mg reduces acute brain and spinal edema.

[0085] For the treatment of mononucleosis, Applicants have successfully administered to a patient suffering from a particularly bad case for some time, Vitamin C and hyaluronic acid and the patient rapidly recovered.

[0086] One form of hyaluronic acid and/or sodium hyaluronate suitable for use with Applicant's invention is a fraction supplied by Sterivet Laboratories Limited. One such fraction is a 15 ml vial of Sodium hyaluronate 20mg/ml (300mg/vial - Lot 2F3). The sodium hyaluronate fraction is a 2% solution with a mean average molecular weight of about 225,000. The fraction also contains water q.s. which is triple distilled and sterile in accordance with the U.S.P. for injection formulations. The vials of hyaluronic acid and/or sodium hyaluronate may be carried in a Type 1 borosilicate glass vial closed by a butyl stopper which does not react with the contents of the vial.

[0087] The fraction of hyaluronic acid and/or sodium hyaluronate may comprise hyaluronic acid and/or sodium hyaluronate having the following characteristics: a purified, substantially pyrogen-free fraction of hyaluronic acid obtained from a natural source having at least one characteristic selected from the group consisting of the following:

i) a molecular weight within the range of 150,000-225,000;
ii) less than about 1.25% sulphated mucopolysaccharides on a total weight basis;
iii) less than about 0.6% protein on a total weight basis;
iv) less than about 150 ppm iron on a total weight basis;
v) less than about 15 ppm lead on a total weight basis;
vi) less than 0.0025% glucosamine;
vii) less than 0.025% glucuronic acid;
viii) less than 0.025% N-acetylglucosamine;
ix) less than 0.0025% amino acids;
x) a UV extinction coefficient at 257 nm of less than about 0.275;
xi) a UV extinction coefficient at 280 nm of less than about 0.25, and
xii) a pH within the range of 7.3-7.9.

Preferably the hyaluronic acid is mixed with water and the fraction of hyaluronic acid fraction has a mean average molecular weight within the range of 150,000-225,000. More preferably the fraction of hyaluronic acid comprises at least one characteristic selected from the group consisting of the following characteristics:

i) less than about 1% sulphated mucopolysaccharides on a total weight basis;
ii) less than about 0.4% protein on a total weight basis;
iii) less than about 100 ppm iron on a total weight basis;
iv) less than about 10 ppm lead on a total weight basis;
v) less than 0.00166% glucosamine;
vi) less than 0.0166% glucuronic acid;
vii) less than 0.0166% N-acetylglucosamine;
viii) less than 0.00166% amino acids;
x) a UV extinction coefficient at 257 nm of less than about 0.23;
xi) a UV extinction coefficient at 280 nm of less than 0.19; and
xii) a pH within the range of 7.5-7.7

[0088] Other forms of hyaluronic acid and/or sodium hyaluronate may be chosen from other suppliers, for example those described in the prior art documents previously referred to. In addition Applicants have successfully employed sodium hyaluronate produced and supplied by LifeCore™ Biomedical, Inc. having the following specifications

Characteristics	Specification
Appearance	White to cream colored particles

(continued)

Characteristics	Specification
Odor	No perceptible odor
Viscosity Average Molecular Weight	< 750,000 Daltons
UV/Vis Scan, 190-820nm	Matches reference scan
OD, 260nm	< 0.25 OD units
Hyaluronidase Sensitivity	Positive response
IR Scan	Matches reference
pH, 10mg/g solution	6.2 - 7.8
Water	8% maximum
Protein	< 0.3 mcg/mg NaHy
Acetate	< 10.0 mcg/mg NaHy
Heavy Metals, maximum ppm	
As 2.0 | Cd 5.0 | Cr 5.0 | Co 10.0 | Cu 10.0 | Fe 25.0	Pb 10.0 | Hg 10.0 | Ni 5.0
Microbial Bioburden	None observed
Endotoxin	< 0.07EU/mg NaHy
Biological Safety Testing	Passes Rabbit Ocular Toxicity Test

[0089] The following references teach hyaluronic acid, sources thereof and processes of the manufacture and recovery thereof.

[0090] United States Patent 4,141,973 teaches hyaluronic acid fractions (including sodium salts) having:

"(a) an average molecular weight greater than about 750,000, preferably greater than about 1,200,000 - that is, a limiting viscosity number greater than about 1400 $cm^3/g.$, and preferably greater than about 2000 $cm^3/g.$;
(b) a protein content of less than 0.5% by weight;
(c) ultraviolet light absorbance of a 1% solution of sodium hyaluronate of less than 3.0 at 257 nanometers wavelength and less than 2.0 at 280 nanometers wavelength;
(d) a kinematic viscosity of a 1% solution of sodium hyaluronate in physiological buffer greater than about 1000

centistokes, preferably greater than 10,000 centistokes;
(e) a molar optical rotation of a 0.1 - 0.2% sodium hyaluronate solution in physiological buffer of less than -11 X 10^3 degree - cm^2/mole (of disaccharide) measured at 220 nanometers;
(f) no significant cellular infiltration of the vitreous and anterior chamber, no flare in the aqueous humor, no haze or flare in the vitreous and no pathological changes to the cornea, lens, iris, retina, and choroid of the owl monkey eye when one milliliter of a 1% solution of sodium hyaluronate dissolved in physiological buffer is implanted in the vitreous replacing approximately one-half the existing liquid vitreous, said HUA being
(g) sterile and pyrogen free and
(h) non-antigenic."

[0091] Canadian Letters Patent 1,205,031 (which refers to United States Patent 4,141,973 as prior art) refers to hyaluronic acid fractions having average molecular weights of from 50,000 to 100,000; 250,000 to 350,000; and 500,000 to 730,000 and discusses processes of their manufacture.

[0092] Where high molecular weight hyaluronic acid (or sodium hyaluronate) is used, it must be diluted to permit administration and ensure no intramuscular coagulation.

[0093] One formulation of Ascorbic Acid (Vitamin C) injection USP is manufactured by Steris Laboratories, Inc., Phoenix, Arizona, 85043 U.S.A. and comprises 22 mg/ml (equivalent to sodium ascorbate 250 mg/ml) in 30ml, 50ml, or 100ml individual containers, 30ml size being preferred.

[0094] Thus Applicant has combined hyaluronic acid and/or sodium hyaluronate with medicinal and/or therapeutic agents for the treatment of conditions and diseases with totally unexpected results:

[0095] For Example

Condition/Disease	Chemicals & Drugs
1. Hair growth	minoxidil - combination - grow more hair when applied topically
2. Herpes, canker sore, shingles	nonionic surfactants, e.g. nonoxynol-9 and anionic, (e.g. cetyl pyridinium chloride) and cationic (e.g. benzalkonium chloride), surfactants
3. Renal failure, cardiac insufficiency, hypertension, edema	diuretics - furosemide
4. Infection, acne, mononucleosis	antibiotics, antibacterials, antimicrobials, etc., ascorbic acid and hyaluronic acid
5. Transplants	cyclosporins
6. Inflammation, elimination of tumour break down material (toxins and debris), decreasing side effects, relief of pain (e.g. back pain)	non-steroidal anti-inflammatories, NSAID e.g. diclofenac, indomethacin, piroxicam, ibuprofen, tromethamine salt of Ketorolac, naproxen,
7. Detoxification	enema, detoxifying agent, peritoneal dialysis
8. Bronchodilation	bronchodilators, e.g. beclomethasone diproprionate (sodium cromoglycate although not specifically a bronchodilator), theophylline
9. Vascular ischemia	treat limbs in respect of diabetes, Berger's disease, etc. with suitable medicine e.g. Trental
10. HIV (AIDS)	DMSO, Vitamin C, NSAID (e.g. indomethacin, naproxen, ketorolac tromethamine) interferon, Vibramycin™, (doxcycline), tetracycline
11. Diabetes	insulin
12. Post-menopause	estrogens replacement
13. Prevention of topical infection	antimetabolites (e.g. sulfonamides)
14. Hypertension, cardiac insufficiency	calcium channel blockers e.g. - Nifedipine β-Blockers e. g. atenolol, propranolol
15. Prostaglandin	acetylsalicylic acid
16. Enhance oxygenation of tissue by perfusion fluid bathing the tissue (for transplantation purposes)	perfusate
17. Psoriasis	methotrexate

Applicants have now provided uses according to the claims which appear to enhance a patient's life expectancy and quality of life (even those patients not responding to the usual treatments). Applicants have successfully treated patients with their invention, improving for example macrophage function, to enable the body to eliminate the tumor cells, dead tumor waste, debris, and toxins.

EXAMPLES

[0096] The following examples are offered to illustrate Applicant's invention. The hyaluronic acid referred to herein also includes sodium hyaluronate.

CASE I:

[0097] The patient had an arterial line and subcutaneous port installed at the time of the original abdominal surgery. He came to see Dr. Falk and it was noted that there was redness, in duration and swelling around the subcutaneous port. The patient had a febrile response and elevation of his leukocytes.

[0098] A £ 14 gauge plastic cannula was inserted into the area and 75 cc of purulent material was drained and cultured growing E.coli and Pseudomonas aeruginosa. Dr. Falk treated him by irrigating the site with a combination of hyaluronic acid with ampicillin, hyaluronic acid with flagyl., and hyaluronic acid with keflosporin. Thus the wound was irrigated on a daily basis with 1 gram of ampicillin with 50 mgs. of hyaluronic acid, 500 mgs. flagyl with 50 mgs. of hyaluronic acid and 1 gram of Ancef with hyaluronic acid. During the first 2 - 3 days irrigation it was possible to continue to aspirate purulent material from the subcutaneous site. Within 5 days there was no purulent material remaining and there was just fluid present and by the end of the week there was no residual infection present. The port-a-cath continued to function over the next three months of the patient life.

[0099] This is cited as an example of anti-bacterial agents with added hyaluronic acid producing better penetration of the various different anti-bacterial drugs into the site of infection and one would have to postulate that there was improved penetration into the bacteria themselves.

CASE II:

[0100] This patient was operated on June 1st, 1989 and a resection was performed of a portion rectum and sigmoid colon, and the small intestine. Post-operatively on day 7 he was noted to have swelling and induration in the wound tissue and two sites of purulent material were drained. He was treated subsequently with local irrigation with ampicillin 1 gram combined with 50 mgs. hyaluronic acid and 500 mgs. of flagyl combined with hyaluronic acid. These two areas of infection cleared of any bacterial contamination within 4 days. The usual time required would be in the order of a number of weeks.

CASE III:

[0101] This patient with cancer of the breast has an infected Hickman Line. This is an indwelling plastic catheter 39 in the subclavian vein. This infection was present subcutaneously with purulent material coming from the site of the entry of the plastic cannula. In this situation Dr. Falk injected ampicillin 1 gram and 50 mgs. of hyaluronic acid directly adjacent to the plastic catheter. In addition the patient received flagyl intravenously with added hyaluronic acid. The infection cleared and the catheter was presented in a matter of 4 days.

CASE IV:

[0102] This man developed an abscess on the right upper quadrant of his abdomen, in the anterior abdominal wall. This was drained in hospital but continued to be a problem. Dr. Falk has now discharged him and begun to irrigate this with ampicillin 500 mg daily and 200 mg of hyaluronic acid. While this abscess was drained and therefore should have recovered eventually, it had taken a longer period of time than one would have anticipated. The abscess grew both staphlyococcus aureus and e. coli.

[0103] After 2 days of irrigation with ampicillin and hyaluronic acid as described, the cavity was clean, free of infection and beginning to granulate over nicely. Dr. Falk continued to treat him during the week and it healed satisfactorily.

[0104] In other patients alpha 2- interferon was combined with hyaluronic acid and applied to a patients canker sores and the sores rapidly cleared up.

[0105] In another patient, methotrexate was carried in hyaluronic acid and applied topically to a patient with psoriasis. The formulation was absorbed and the psoriasis cleared.

[0106] In ten other patients suffering from herpes simplex type I and II, the application of an effective amount of

nonoxynol-9 [nonylphenoxy polyethoxy ethanol] (Delfen™) combined with hyaluronic acid and/or salts thereof to the effected areas 2 to 3 times daily gave immediate relief of the symptoms (pain) and disappearance of the lesions.

[0107] In at least two patients, an effective amount of nonoxynol-9 for treating herpes zoster (shingles) was combined with hyaluronic acid and/or salts thereof and was successfully employed to treat the herpes zoster (shingles).

CASE V:

[0108] A dentist with melanoma, age 51, developed acute herpes zoster in the 9th thorasic dermital on the left side of his body. He was in excruciating pain, not relieved by classical medications. Dr. Falk asked him to take orally cyclofur as an antiviral but he did not begin this immediately. However, Dr. Falk also indicated that he should take "Delfen™" and "LifeCore™" hyaluronic acid, mix equal portions and then apply this topically. He did this and had immediate relief of pain within 5 minutes. The pain has remained absent for the next 4 days. In addition, the lesions of herpes zoster immediately began to disappear within the first 24 hours and now, 5 days later, none are apparent. This is a dramatic response suggesting a major antiviral affect of this combination, with the hyaluronic acid obviously enhancing penetration.

CASE VI:

[0109] This female (age 18) patient was treated for infectious mononucleosis. Three months of testing the patient resulted in positive heterophile antibody tests. Patient had no energy. The patient was given 50gm of Vitamin C and 300mg of hyaluronic acid. Within sixteen hours of the treatment her energy increased dramatically and within two weeks the heterophile antibody test became negative.

CASE VII:

[0110] In normal healthy individuals, it was observed that adding hyaluronic acid to furosemide (Lasix™) administered at a dose of 20mg intravenously with 300mg of hyaluronic acid, there was an increase of urine excretion by 3 to 5 fold as compared to that observed with furosemide (Lasix™) alone. This is cited as evidence that hyaluronic acid increases penetration/permeation of the drug and thus facilitates its function.

CASE VIII:

[0111] This balding patient applied minoxidil (Rogaine) topically to his scalp. There was minimal or little hair growth. Subsequently, the minoxidil was applied together with hyaluronic acid continuously every 2 to 3 days. As a result, this patient's hair has grown fuller and more rapidly.

CASE IX:

[0112] This man had a chronic abscess cavity in his pelvis with a bowel obstruction which necessitated an operation on January 5, 1990. At that time the cavity was irrigated out and drained through the perineum. He had an uneventful post-operative course and was discharged from hospital on January 18, 1990.

[0113] However, subsequently he developed a fever and because this had been a large cavity in the pelvis, it now drained through the lower anterior part of his abdominal incision. This occurred two weeks prior to the present visit.

[0114] Dr. Falk assessed him. This is a large cavity and he thought that this would take 4 to 6 weeks to close. Dr. Falk instituted daily irrigations during the 5 day working week with ampicillin, flagyl and hyaluronic acid using 500mg of ampicillin and 500mg of flagyl. This is a very benign form of treatment in contrast to what Dr. Falk would usually use which would consist of irrigation and packing the area open.

[0115] When seen later, the abscess cavity had closed over. The patient advised that the visiting nurse on the weekends had difficulty putting a catheter into this cavity over Saturday and Sunday and in fact could not gain entrance of the catheter. Dr. Falk concluded that the cavity had granulated in from the "bottom up" but has done so much more rapidly than he would have anticipated. In view of the fact that this is a chronic cavity in a patient who has had a chronic and ongoing problem in the pelvis, this is clearly an unanticipated result with a much more rapid and better resolution of a chronic abscess cavity than anticipated.

[0116] Dr. Falk has instructed the patient to call if he develops any temperature subsequent to this. He has had a mild itching sensation over his skin which Dr. Falk believes is probably a reaction to cold and for which he gave him an ointment to be applied daily.

CASE X:

[0117] This man has a mesothelioma following surgical resection and then adjuvant treatment. It is now seven years since the initial diagnosis. In the spring of this year he developed a recurrence while in Florida. Although Dr. Falk has biopsied this three times, Dr. Falk has never obtained cells diagnostic of malignancy. However, clinically the situation is very clear from the CAT scan, liver function test and ultrasound.

[0118] This patient has been treated with phloretin in hyaluronic acid, and heat to the area. Initially, he did not show a major response. However, on the last occasion he received no chemotherapy and only phloretin in hyaluronic acid with a higher dose of hyaluronic acid. He has had a major response and has had major problems with accumulation of fluid, Dr. Falk believes, secondary to tumor breakdown. The tumor breakdown is clearly apparent on the sonographic assessment; here there is actual liquification of the tumor.

[0119] During his present stay, he was treated one day with hyperthermia and received phloridzin in hyaluronic acid. However, he required an additional two days of treatment with Vitamin C in hyaluronic acid to assist in detoxification. He also received additional diuretics Lasix™ (furosemide) with hyaluronic acid.

[0120] His creatinine which was 400m mols/l has decreased to 155y mols/l (kidney function tests- went from high to almost normal). Dr. Falk has instructed him regarding further management. Dr. Falk does not think the patient will require major further therapy as Dr. Falk thinks the majority of this tumor has been destroyed, through his own immune response, the antibody and the soluble mediators being allowed to enter into the tumor by hyaluronic acid.

[0121] In July, 1990 moderate ascites (fluid in body) occurred. The patient was given furosemide (Lasix™) and hyaluronic acid, indomethacin and hyaluronic acid. The patient's urine output increased substantially and the problem cleared.

CASE XI:

[0122] A 37 year old female had a carcinoma of the cervix which was a class IIIB at the time of diagnosis. She was treated by radiation at the Cross Cancer Centre, unsuccessfully, and developed further growth of the tumor which was diagnosed approximately 1 to 2 months after the radiotherapy. She was then seen by Dr. Walde at the Sault Ste. Marie hospital. He administered epirubicin, cisplatinum at high doses and did produce regression of the tumor as assessed by intravaginal assessment and biopsy, but apparently there was regrowth and worsening of the pain with partial ureteric obstruction demonstrated as shown by a CT scan of the abdomen and pelvis done June 28, 1990.

[0123] At laparotomy, the patient had extensive tumor with major areas of necrosis but tumor extending to and involving the left common iliac artery and vein producing obstruction of the vein, the tumor was considered not resectable for surgical cure because of its extent in the lateral true and false pelvis to the pelvic wall. This was assessed by a urological and two general oncological surgeons.

[0124] For this reason and because of imminent rectal obstruction, a colostomy was performed. In addition, the urological surgeon established an ileal conduit.

[0125] This patient was in excruciating pain continuously for several weeks prior to and after the surgical procedure. This necessitated high doses of intravenous morphine with only partial control of the pain. On July 8th she was noted to have a major febrile reaction and a CAT scan that day showed an abscess in the left pelvis. This was drained under CAT scan localization and the patient was placed on systemic antibiotics with only slight improvement in her infectious symptoms.

[0126] She was brought to Dr. Falk on Wednesday, July 11th. She received 1gm of ampicillin through the draining catheter for the abscess with 500mg of hyaluronic acid. In addition, she received 1mg of ampicillin intravenously and ancef and flagyl systemically in 500mg "LifeCore™" hyaluronic acid. She also received 100mg of indomethacin with 500mg LifeCore™ hyaluronic acid intravenously. Within 12 hours her pain had dramatically decreased, all infective symptoms were eliminated and the drainage from the abscess cavity had almost stopped. Her massively enlarged left leg due to venous and lymphatic obstruction improved to almost normal size within a 12 hour period of time.

[0127] The patient was subsequently treated further with the same regimen for the next 3 days resulting in total relief of pain and continued improvement in her status, to the point where she could be discharged from the hospital on July 18th without anti-biotic therapy. Her systemic analgesia with morphine agents had been eliminated. There was no hyperthermia and no cytosis chemotherapy and/or Oncostatin (phloretin) utilized in this patient. She received antioxidant therapy with hyaluronic acid concomitently with the indomethacin-hyaluronic acid. This patient has demonstrated a very dramatic improvement emphasizing that the indomethacin-hyaluronic acid is targeting specifically to pathological tissue improving macrophage function at this site and allowing the body's immune system to perform appropriate tumor destruction.

CASE XII:

[0128] A male patient suffering from HIV (AIDS) was treated. with indomethacin (NSAID), Vitamin C, interferon and DMSO and/or hyaluronic acid and unexpectedly the patient is steadily improving.

CASE XIII:

[0129] A male patient suffering from kyphosis suffered from constant back pain. Taking analgesics orally and rubbing back preparations onto his back, did little to alleviate the back. pain. When NSAIDS in hyaluronic acid (sodium hyaluronate) were applied directly to the back, the back pain eased and disappeared.

[0130] With indomethacin (dissolved in N-methyl glucamine) and naproxen both dissolved in hyaluronic acid, the patient experienced side effects. However, with Toradol™ (the [+/-] form tromethamine salt of ketorolac - a prostaglandin biosynthesis inhibitor and analgesic and anti-inflammatory, the back pain eased and disappeared for some time and there were no side effects.

CASE XIV:

[0131] This male patient was diagnosed with HIV (AIDS) and as a possible result thereof, an undetermined neoplastic disorder in the lungs. Before treatment, the patient was near death; white cell count was 1.4 X 10^9/litre. The patient was treated intravenously with indomethacin (300mg), Vitamin C (50gm daily) and hyaluronic acid (sodium hyaluronate) (300mg). After treatment, the patient's platelet count rose to 65 X 10^9/litre. and his white cell. count rose to 8.2 X 10^9/litre. His lymphocytes doubled.

Further Tests (Animal)

[0132] Further tests were conducted on animals (rats) with the indicated results:

[0133] Enhanced Activity of Antibiotics with hyaluronic acid. A chronic abscess rat model was used. Sprague Dawley Rats were used. Pellets of bacteria were inserted into each of the bellies of the rats and then the rats were treated as indicated. In this model therapeutic activity of gentamycin was compared to gentamycin in hyaluronic acid the results demonstrate a statistically significant improvement by the combination over the antibiotic alone. In this regard lower doses of antibiotic in antibiotic refractory situations were required as a result of the antibiotic being administered with hyaluronic acid. Please refer to Figure 1/1 of the drawings.

[0134] In another animal test (Grafts from ACI strain rats (black) to Lewis Strain rats (white)), enhancement of graft survival was found by combinations of immune suppressors and hyaluronic acid (HA) administered to the Lewis Strain rats Graft survival depends in major part on the ability to suppress graft rejection with immunosuppressive agents optimum activity of these agents is seldom achieved as they are not delivered to the graft site in effective concentrations; combinations of the agent with hyaluronic acid overcomes this difficulty. Optimization of immunosuppressive/graft survival activity by combination of specific agents with hyaluronic acid is achieved. A standard rat skin graft rejection model was used. Cyclosporin was the immunosuppressant used. The results indicate that hyaluronic acid significantly increased cyclosporin induced graft survival.

GRAFT SURVIVAL OF DIFFERENT TREATMENTS (JULY 12, 1990)			
CYA+HA#	days	CyA#	days
1	20	7	20
2	19	8	20
3	19	9	20
4	20	10	19
5	19	11	19
6	20	12	20
13	21	20	19
14	19	21	17
15	18	22	14
16	20	23	14
17	20	24	14
18	20	25	19

(continued)

GRAFT SURVIVAL OF DIFFERENT TREATMENTS (JULY 12, 1990)			
CYA+HA#	days	CyA#	days
19	20		
mean	19.615	17.917	
SE	0.213	0.723	
CyA+HA vs. CyA = P value, one-way ANOVA = <0.05 (=0.0287) LSDMRT = <0.05			
CyA = Cyclosporin			
HA = Hyaluronic Acid			

[0135] As many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

Claims

1. The use of:

(1) a medicinal and/or therapeutic agent and
(2) hyaluronic acid and/or sodium hyaluronate in the manufacture of a pharmaceutical composition for treating a disease or condition in a therapy wherein a therapeutically effective amount of said medicinal and/or therapeutic agent (component (1)) is to be administered to a human, together with the hyaluronic acid and/or sodium hyaluronate in an amount sufficient to provide a dosage greater than 10mg/70kg person **characterised in that** the amount of component (2) is immediately available to transport component (1) at the site to be treated, and, is an effective non-toxic amount to facilitate the transport of component (1) through the tissue (including scar tissue) at the site to be treated and through the cell membranes at the individual cells to be treated, and **in that:**

(i) when the disease or condition is herpes canker sores or shingles, component (1) is a non-ionic surfactant;
(ii) when the disease or condition is renal failure, cardiac insufficiency, hypertension and edema, component (1) is a diuretic;
(iii) when the disease or condition is infection or acne, component (1) is an agent selected from antibiotics, antibacterials and antimicrobials;
(iv) when the disease or condition is mononucleosis, component (1) is ascorbic acid;
(v) when the disease or condition relates to the transplantation of an organ, component (1) is a cyclosporin;
(vi) when the disease or condition is inflammation or pain, or arises from toxins and debris resulting from tumour breakdown or requires the decrease of side effects of giving an NSAID, component (1) is an NSAID;
(vii) when the disease or condition is the toxification of the body, component (1) is a detoxifying agent;
(viii) when the disease or condition requires bronchodilation, component (1) is a bronchodilator;
(ix) when the disease or condition is vascular ischemia, component (1) is trental;
(x) when the disease or condition is HIV or AIDS, component (1) is selected from the agents consisting of Ascorbic Acid, NSAID, doxocycline, tetracycline and combinations thereof;
(xi) when the disease or condition is diabetes, component (1) is insulin;
(xii) when the disease or condition is topical infection or the prevention thereof, component (1) is an antimetabolite;
(xiii) when the disease or condition is post-menopause, component (1) is an estrogen replacement;
(xiv) when the disease or condition is hypertension or cardiac insufficiency, component (1) is a calcium channel blocker;
(xv) when the disease or condition requires prostaglandin synthesis inhibition, component (1) is an NSAID;
(xvi) when the disease or condition requires enhanced oxygenation of tissue by perfusion fluid, component (1) is perfusate; and
(xvii) when the disease or condition is psoriasis, component (1) is methotrexate.
(xviii) when the disease or condition is hair loss component (1) is minoxidil.

2. The use of claim 1 wherein the disease or condition is herpes canker sores or shingles and component (1) is a non-ionic surfactant.

3. The use of claim 1 wherein the disease or condition is renal failure, cardiac insufficiency, hypertension and edema and component (1) is a diuretic.

4. The use of claim 1 wherein the disease or condition is infection or acne and component (1) is an agent selected from antibiotics, antibacterials and antimicrobials.

5. The use of claim 1 wherein the disease or condition is mononucleosis and component (1) is ascorbic acid.

6. The use of claim 1 wherein the disease or condition relates to the transplantation of an organ and component (1) is a cyclosporin.

7. The use of claim 1 wherein the disease or condition is inflammation or pain, or arises from toxins and debris resulting from tumour breakdown or requires the decrease of side effects of giving an NSAID and component (1) is an NSAID.

8. The use of claim 1 wherein the disease or condition is the toxification of the body and component (1) is a detoxifying agent.

9. The use of claim 1 wherein the disease or condition requires bronchodilation and component (1) is a bronchodilator.

10. The use of claim 1 wherein the disease or condition is vascular ischemia and component (1) is trental.

11. The use of claim 1 wherein the when disease or condition is HIV or AIDS and component (1) is selected from the agents consisting of Ascorbic Acid, NSAID, doxocycline, tetracycline and combinations thereof.

12. The use of claim 1 wherein when the disease or condition is diabetes and component (1) is insulin.

13. The use of claim 1 wherein when the disease or condition is topical infection or the prevention thereof and component (1) is an anti-metabolite.

14. The use of claim 1 wherein when the disease or condition is post-menopause, and component (1) is an estrogen replacement.

15. The use of claim 1 wherein when the disease or condition is hypertension or cardiac insufficiency and component (1) is a calcium channel blocker.

16. The use of claim 1 wherein when the disease or condition requires prostaglandin synthesis inhibition and component (1) is an NSAID.

17. The use of claim 1 wherein when the disease or condition requires enhanced oxygenation of tissue by perfusion fluid and component (1) is perfusate.

18. The use of claim 1 wherein when the disease or condition is psoriasis and component (1) is methotrexate.

19. The use of claim 1 wherein the disease or condition is hair loss and component (1) is minoxidil.

20. The use of claim 1, 7, 11 or 16 wherein the NSAID is selected from diclofenac, indomethacin, piroxicam, ibuprofen, tromethamine salt of ketorolac and naproxen.

21. The use of claim 1 or claim 9 wherein the bronchodilator is selected from beclomethasone diproprionate, theophylline and sodium cromoglycate.

tique pour le traitement d'une maladie ou d'un état lors d'une thérapie dans laquelle une quantité efficace sur le plan thérapeutique dudit agent médicinal et/ou thérapeutique (composant (1)) est administrée à un homme, conjointement avec l'acide hyaluronique et/ou l'hyaluronate de sodium en une quantité suffisante pour procurer une dose supérieure à 10 mg/personne de 70 kg **caractérisée en ce que** la quantité du composant (2) est immédiatement disponible pour transporter le composant (1) au site à traiter, et est une quantité efficace non toxique pour faciliter le transport du composant (1) au travers du tissu (y compris un tissu cicatriciel) au site à traiter et au travers des membranes cellulaires au niveau des cellules individuelles à traiter, et **en ce que** :

(i) lorsque la maladie ou l'état est des aphtes ou des zonas d'herpès, le composant (1) est un tensioactif non ionique;
(ii) lorsque la maladie ou l'état est une insuffisance rénale, une insuffisance cardiaque, une hypertension et un oedème, le composant (1) est un diurétique;
(iii) lorsque la maladie ou l'état est une infection ou un acné, le composant (1) est un agent sélectionné parmi des antibiotiques, des agents antibactériens et des agents antimicrobiens;
(iv) lorsque la maladie ou l'état est la mononucléose, le composant (1) est l'acide ascorbique;
(v) lorsque la maladie ou l'état concerne la transplantation d'un organe, le composant (1) est une cyclosporine;
(vi) lorsque la maladie ou l'état est une inflammation ou une douleur, ou a pour origine des toxines et des débris provenant d'une rupture de tumeur ou requiert la diminution des effets secondaires de l'administration d'un AINS, le composant (1) est un AINS;
(vii) lorsque la maladie ou l'état est l'intoxication du corps, le composant (1) est un agent de détoxification;
(viii) lorsque la maladie ou l'état requiert une bronchodilatation, le composant (1) est un bronchodilatateur;
(ix) lorsque la maladie ou l'état est une ischémie vasculaire, le composant (1) est le trental;
(x) lorsque la maladie ou l'état est le VIH ou le SIDA, le composant (1) est sélectionné parmi les agents comprenant l'acide ascorbique, un AINS, la doxocycline, la tétracycline et des combinaisons de ceux-ci;
(xi) lorsque la maladie ou l'état est un diabète, le composant (1) est l'insuline;
(xii) lorsque la maladie ou l'état est une infection topique ou la prévention de celle-ci, le composant (1) est un anti-métabolite;
(xiii) lorsque la maladie ou l'état est l'après-ménopause, le composant (1) est un substitut d'oestrogènes;
(xiv) lorsque la maladie ou l'état est une hypertension ou une insuffisance cardiaque, le composant (1) est un agent bloquant les canaux calciques;
(xv) lorsque la maladie ou l'état requiert une inhibition de la synthèse de prostaglandines, le composant (1) est un AINS;
(xvi) lorsque la maladie ou l'état requiert une oxygénation accrue d'un tissu par un fluide de perfusion, le composant (1) est un perfusat; et
(xvii) lorsque la maladie ou l'état est le psoriasis, le composant (1) est le méthotrexate;
(xviii) lorsque la maladie ou l'état est une perte de cheveux, le composant (1) est le minoxidil.

2. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est des aphtes ou des zonas d'herpès et le composant (1) est un tensioactif non ionique.

3. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est une insuffisance rénale, une insuffisance cardiaque, une hypertension et un oedème et le composant (1) est un diurétique.

4. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est une infection ou un acné et le composant (1) est un agent sélectionné parmi des antibiotiques, des agents antibactériens et des agents antimicrobiens.

5. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est la mononucléose et le composant (1) est l'acide ascorbique.

6. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état concerne la transplantation d'un organe et le composant (1) est une cyclosporine.

7. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est une inflammation ou une douleur, ou a pour origine des toxines et des débris provenant d'une rupture de tumeur ou requiert la diminution des effets secondaires de l'administration d'un AINS et le composant (1) est un AINS.

8. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est l'intoxication du corps et le composant

(1) est un agent de détoxification.

9. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état requiert une bronchodilatation et le composant (1) est un bronchodilatateur.

10. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est une ischémie vasculaire et le composant (1) est le trental.

11. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est le VIH ou le SIDA et le composant (1) est sélectionné parmi les agents comprenant l'acide ascorbique, un AINS, la doxocycline, la tétracycline et des combinaisons de ceux-ci.

12. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est un diabète et le composant (1) est l'insuline.

13. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est une infection topique ou la prévention de celle-ci et le composant (1) est un anti-métabolite.

14. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est l'après-ménopause et le composant (1) est un substitut d'oestrogènes.

15. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est une hypertension ou une insuffisance cardiaque et le composant (1) est un agent bloquant les canaux calciques.

16. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état requiert une inhibition de la synthèse de prostaglandines et le composant (1) est un AINS.

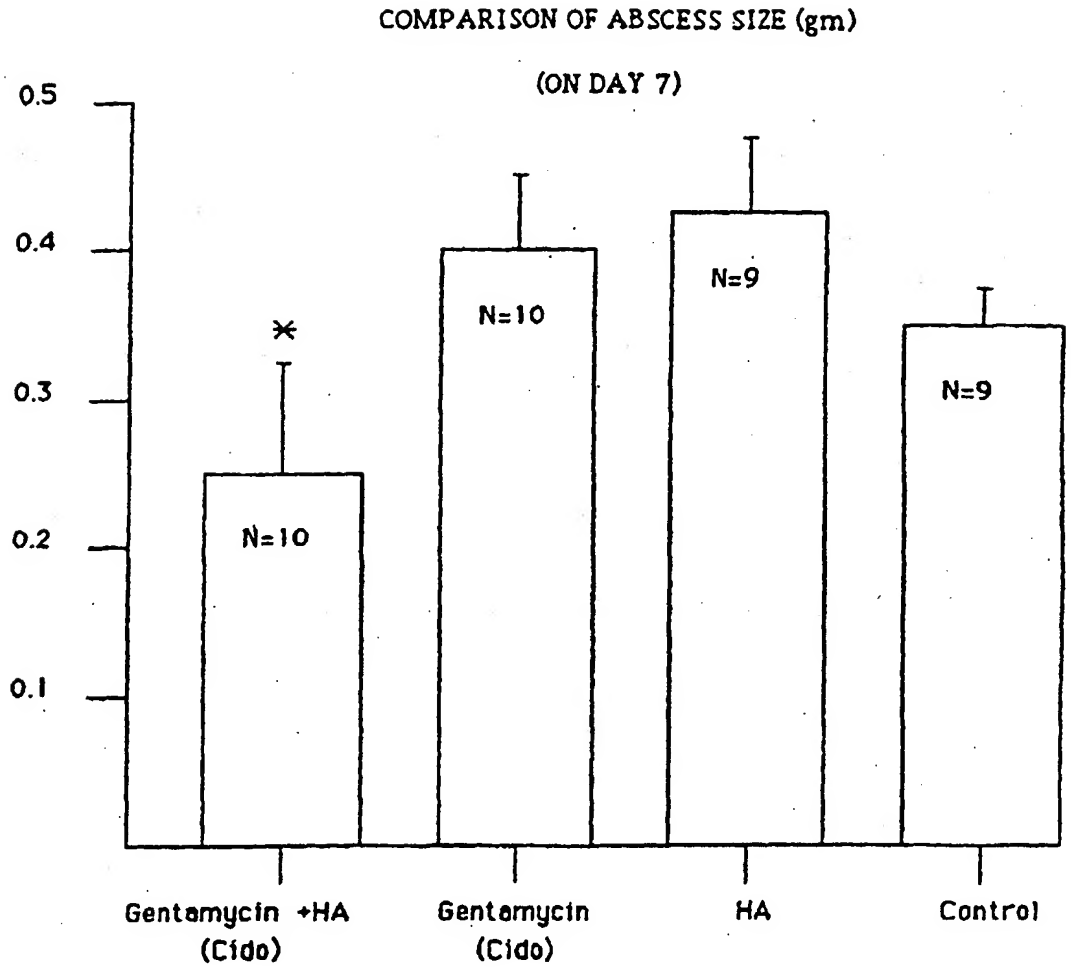
17. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état requiert une oxygénation accrue d'un tissu par un fluide de perfusion et le composant (1) est un perfusat.

18. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est le psoriasis et le composant (1) est le méthotrexate.

19. Utilisation suivant la revendication 1, dans laquelle la maladie ou l'état est une perte de cheveux et le composant (1) est le minoxidil.

20. Utilisation suivant la revendication 1, 7, 11 ou 16, dans laquelle le AINS est sélectionné parmi le diclofénac, l'indométhacine, le piroxicam, l'ibuprofène, le sel trométhamine de kétorolac et le naproxène.

21. Utilisation suivant la revendication 1 ou la revendication 9, dans laquelle le bronchodilatateur est sélectionné parmi le dipropionate de béclométhasone, la théophylline et le cromoglycate de sodium.



*P< 0.05, vs. Cido and HA groups. (LSDMRT, Dunken's)
Gentamycin (Cido) and/or HA were injected I.M., B.I.D. for 5 days postoperatively.

Cido: 2mg/kg/day (3 mg/kg/day for human being)
HA: 4mg/kg/day (equivalent to 280mg/day for 70kg human being)